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Letter to the Editor

NTD Phenotypes in Infants and Fetuses Whose Mothers Used Multivitamins Containing Folic Acid in Early Pregnancy Compared to Those Who Did Not

To the Editor:

Studies have shown as much as a 70% reduction in risk for neural tube defects (NTDs) associated with maternal periconceptional intake of vitamins (including multivitamins) containing folic acid [MRC, 1991; Czeizel and Dudas, 1992]. Nevertheless, some pregnancies in which women periconceptionally consumed vitamins containing folic acid still produced NTDs. Seller 1995 recently explored whether specific neural tube closure sites were more likely to occur among 13 infants or fetuses whose mothers received folic acid supplementation in early pregnancy. Seller found no absence or excess of any particular phenotype among this small study group of recurrent NTDs.

Extending Seller's reasoning, we examined a large population-based cohort of occurrent NTD-affected pregnancies to determine whether NTD phenotypes were different among offspring of women who consumed multivitamins containing folic acid, compared to women who did not consume such supplements, in early pregnancy. With these data, we previously reported a reduction in risk for all NTDs [Shaw et al., 1995] as well as a reduction in risk for NTDs occurring in combination with other major structural congenital anomalies [Khoury et al., 1996] associated with maternal periconceptional vitamin use. The goal of this analysis was to extend those findings using more detailed phenotypic information about anatomic and pathogenetic subclasses of NTDs.

Data used for this analysis were described elsewhere [Shaw et al., 1995]. Eligible NTD (anencephaly, spina bifida cystica, craniorachischisis, or iniencephaly) cases were singleton fetuses, including those electively terminated, and liveborn infants diagnosed with a NTD among the cohort of 708,129 California births (includes fetal deaths) between June 1989 and May 1991. Ascertained were 653 singleton infants or fetuses with a NTD. Excluded were women who only spoke languages other than English or Spanish, as well as 11 women who had a previous NTD-affected pregnancy. Interviews were completed with mothers of 538 (87.8%) cases.

Women were asked whether they used vitamin supplements in the 3 months before conception, 3 months after conception, and the subsequent 2 trimesters of pregnancy. All cases were subgrouped by a medical geneticist (EJL), first as either isolated or nonisolated based on the presence and nature of accompanying congenital anomalies [see Shaw et al., 1994 for more description about classification]. An infant or fetus with a NTD and an accompanying major anomaly that was not a dysplasia, deformation, disruption, or a consequence of the NTD was considered nonisolated, and the remainder isolated. Spina bifida cases were further subgrouped based on anatomic location of the spinal defect, "high" (upper bony extent of defect above the 12 thoracic vertebra) or "low" (below the 11th thoracic vertebra), and on whether the defect was "open" or covered with full-thickness skin.

As displayed in Table I, no particular phenotype was substantially more, or less (based on comparing percentages across each row), common among the offspring of women who reported using vitamins containing folic acid beginning in the 3 months before conception (nearly all of whom continued use throughout pregnancy) or began use in the first trimester, compared to those women who did not use any vitamins in the periconceptional period 3 months before through 3 months after conception. Excluding ten cases with trisomies did not alter the results shown. Stratification on the basis of infant/fetal sex or maternal education also did not produce results substantially different from those shown in Table I. Analyses specific for non-Hispanic whites (based on maternal race) suggested a slightly smaller proportion of "high" spina bifida defects in the infants or fetuses of mothers who began using vitamins in the 3 months before conception compared to the nonusers of vitamins. Data were too sparse to investigate adequately other specific race/ethnic groups. Examining NTD phenotypes across increasing quartile levels of periconceptional dietary in-

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take of folate also did not identify any substantial differences.

TABLE I. NTD Phenotypes in Offspring of Mothers Who Used or Did Not Use Multivitamin Supplements in the Periconceptional Period

	Multivitamin use					
	Used 3 months before conception		Started use in first trimester		No use	
All cases (no.)	83		236		207	
	N	%[a]	N	%[a]	N	%[a]
Anencephaly	35	42.2	103	43.6	73	35.3
Isolated	33	94.3	88	85.4	61	83.6
Non-isolated	2	5.7	15	14.6	12	16.4
Spina bifida[b]	46	55.4	121	51.3	123	59.4
Skin-covered	3	6.5	13	10.7	21	17.1
Open, not skin-covered	34	73.9	91	75.2	95	77.2
Isolated	29	85.3	76	83.5	83	87.4
Non-isolated	5	14.7	15	16.5	12	12.6
Isolated	38	82.6	98	81.0	102	82.9
Non-isolated	8	17.4	23	19.0	21	17.1
High	5	10.9	16	13.2	16	13.0
Isolated	1	20.0	8	50.0	10	62.5
Low	40	87.0	100	82.6	103	83.7
Isolated	28	70.0	68	68.0	72	69.9
Other NTD[c]	2	2.4	12	5.1	11	5.3

[a]Percentages in each column do not add to 100% because some phenotypes are more specific subsets of others.
[b]For some cases a determination of open vs. skin-covered as well as high vs. low defects could not be made.
[c]Includes 7 combined anencephaly and spina bifida, 15 craniorachischisis, and 3 iniencephaly cases.

Thus, our data are consistent with the observations made by Seller [1995] in that the apparent protective effect of folate appears to be generalized and not specific to a particular site of the developing neural tube.

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